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**TITLE: Comprehensive Study of Acute Effects and Recovery After Concussion**

**PRINCIPAL INVESTIGATOR:** Michael McCrea, PhD, ABPP

**CONTRACTING ORGANIZATION:** Medical College of Wisconsin  
Milwaukee, WI 53226

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14. ABSTRACT With the goal of conducting the most comprehensive study of mTBI to date, we hypothesize that there will be a significant correlation between biomechanical, clinical, neurobiological, and neuroradiological markers of mTBI, which will more fully inform a neurobiopsychosocial model of mTBI. With the goal of baseline testing 900 athletes and enrolling 50 injured athletes and 50 contact and 50 non-contact controls over the course of 3 years, the project is progressing on schedule. We baseline tested 545 football athletes from July 13, 2015 to Aug 21, 2015. We enrolled 12 injured athletes and 5 contact controls within the reporting period of performance ending on September 29 (a total of 25 injured athletes and 15 controls enrolled by date of submission on October 29), with injury and control accrual ongoing during the current football season. All groups are undergoing follow up evaluations within 6 hours of injury, 48 hours after injury, and 8, 15, and 45 days after injury. These evaluations include advanced brain neuroimaging, blood biospecimen collection, and clinical testing measures assessing balance, neurocognition, symptoms, and psychological health. These evaluations will also be correlated with data from the Head Impact Telemetry system (HITS) that athletes are wearing throughout the season. Data analysis preparations are underway with subject matter experts developing advanced database platforms and analysis techniques. Submission to FITBIR is also underway with a full time staff member devoted to creating appropriate UDEs, merging existing CDEs for our initial submission, and working directly with FITBIR staff. Ongoing collaboration with co-investigators and our project partners has guided us to a successful launch of this comprehensive study, which will lead to advancing the science of mTBI and improving clinical care in military, sports, and civilian populations.					
15. SUBJECT TERMS Traumatic brain injury, concussion, biomechanics, head impact measurement, neuroimaging, biospecimens, neurobiopsychosocial					
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## 1. INTRODUCTION:

During the acute phase, mild traumatic brain injury (mTBI) is known to cause serious disruption in normal biological, cognitive, and behavioral function. While research over the last decade has significantly advanced the science of mTBI, a comprehensive neurobiopsychosocial model of mTBI is yet to be achieved. With the goal of conducting the most comprehensive study of mTBI to date, we hypothesize that there will be a significant correlation between biomechanical, clinical, neurobiological, and neuroradiological markers of mTBI, which will more fully inform a neurobiopsychosocial model of mTBI. The overarching aim of this proposal is to investigate the predictive and correlative value of multiple diagnostic and prognostic markers of mTBI in a common injured sample and single study design, including:

- Advanced brain neuroimaging to study changes in brain structure and function
- Blood biomarkers to study changes in brain biochemistry and physiology
- Head impact sensor technologies to study the kinetics and kinematics of concussion and the effects of repetitive, subconcussive head impacts
- Genetic testing to study the influence of genetics on risk of mTBI and post-concussive recovery
- Clinical measures of postconcussive symptoms, neurocognition, balance, psychological health, and other functional capacities to correlate with neurobiological, neuroimaging, biomechanical and genetic markers of injury

Please see section 9 (Appendices, Table 2) for a more detailed summary of this study's technical objectives and specific scientific aims.

## 2. KEYWORDS:

Traumatic brain injury, concussion, biomechanics, head impact measurement, neuroimaging, biospecimens, neurobiopsychosocial

## 3. ACCOMPLISHMENTS:

### What were the major goals of the project?

The major tasks of this project are designed to successfully achieve the specific technical objectives and scientific aims of the study (see Appendices). Please find below a summary of the major tasks, projected timeline, level of completion as of the current reporting period, in accordance with the approved Statement of Work (SOW).

We have completed a significant amount of work toward accomplishment of the major tasks and subtasks for the current reporting quarter, as described below. The major tasks and subtasks for this project are also being coordinated and completed in sequence with planning and execution of the NCAA-DoD Grand Alliance Advanced Research Core (ARC), given the scientific and operational benefits of synchronization between the two projects.

<b>Major Tasks from Statement of Work (SoW)</b>	<b>Timeline (months)</b>	<b>Date or % of completion</b>
<b>Major Task 1:</b> Finalize Project Contracting, Regulatory, and Operational Processes	1-6	100%
<b>Major Task 2:</b> Operationalize Protocol to Achieve Specific Aims (SA) and Technical Objectives 1-4	1-6, Ongoing	90%
<b>Major Task 3:</b> Data Collection (post-IRB approval)	7-48	30%
<b>Major Task 4:</b> Data Management, Analysis & Dissemination	1-48	25%

### **What was accomplished under these goals?**

The tables below provide an update on the status of our progress associated with each of the Major Tasks and Subtasks for the project, in accordance with the approved SoW for this project.

<b>Major Task 1: Finalize Project Contracting, Regulatory, &amp; Operational Processes</b>	<b>Months 1-6</b>
<p><i>Subtask 1 - Contracting</i></p> <ul style="list-style-type: none"> <li>Contracting process completed with MOMRP and CDMRP</li> <li>All required documents and certifications secured from MCW, subaward sites and vendors</li> <li>MCW internal institutional processes completed for award contracting</li> <li>Contracting process completed, funding awarded</li> <li>Subcontract with Banyan Biomarkers was executed on June 30, 2015</li> </ul> <p><i>Subtask 2 – Human Subjects Research</i></p> <ul style="list-style-type: none"> <li>Human subjects research protocol and informed consent finalized, submitted to MCW IRB on March 2, 2015 after alignment with the NCAA-DoD Grand Alliance Advanced Research Core (ARC) protocol</li> <li>Secured all internal safety committee approvals required for MCW IRB submission</li> <li>Initial IRB approval received on April 16, 2015 with subsequent submission to HRPO</li> <li>Prior to data collection, an amendment was submitted to update the roles of Indiana University and MCW Tissue Bank in DNA extraction and analysis per HRPO request; IRB approved on June 2, 2015</li> <li>HRPO approval for initial submission and amendment granted on June 11, 2015</li> <li>Reliance agreement between Banyan Biomarkers and MCW IRB submitted to MCW IRB on July 30, 2015 and approved on Aug 24, 2015</li> <li>Amendments submitted and approved by MCW IRB regarding personality questionnaire changes and head impact sensor company changes</li> <li>Amendment under review as of Sept 29, 2015 regarding discontinuation of i1 mouth guard</li> <li>Reportable events submitted and acknowledged by MCW IRB and HRPO</li> </ul>	

*Subtask 3 – Project Staffing and Operations*

- Project Coordinator and Research Assistant responsibilities assigned
- Appropriate research space and resource allocation to support study activities confirmed
- Developed study operations manual and standard operating procedures for elements of research activity
- Hiring process for additional baseline and biomechanics technicians complete
- Supplies being ordered and collected for research activities
- Hiring complete for FITBIR dedicated staff member
- Assistant professor engaged for expertise in MR and blood biomarkers

*Subtask 4 – Project Management*

- Standing weekly laboratory meeting to facilitate project management and monitor progress
- Established internal system for project operational, regulatory and fiscal management, utilizing MCW eBridge platform and other resources through the MCW Office of Research and Department of Neurosurgery
- Conducted 2-day Kickoff Investigator meeting at MCW in January 2015 to review all scientific and operational elements of study aims, methods, data management, and dissemination plan
- Additional meetings with core subject matter experts occurring at regular intervals to ensure consistency with ARC protocol, plan for data dissemination, and plan for data pipelining

**Major Task 2: Operationalize Protocol to Achieve Specific Aims (SA) and Technical Objectives 1-4**

**Months 1-6**

*Subtask 1 – Overall Protocol Implementation and Management*

- Finalized plan for data collection in the field (baseline and <6 hours postinjury) and on site at MCW (48 hours, days 8, 15, 45 postinjury)
- Engaged participating institutions, including athletic directors, head athletic trainers, and coaches to secure agreements and finalize logistics
- Finalized staffing and operational plan for clinical, neuroimaging, biospecimen and genetic testing procedures (see details below in SA1-SA4)
- Completed baseline testing on 545 athletes from July 13, 2015 to August 21, 2015, including equipping 185 athletes with the Head Impact Telemetry System (HITS) and obtaining atlas MR scans on 11 contact sport subjects
- From August 10, 2015 to September 29, 2015, 12 athletes with concussion and 5 contact controls were enrolled into the post injury protocol (a total of 25 injured athletes and 15 contact controls enrolled by date of submission on October 29, 2015)

*Subtask SA1 – Advanced Neuroimaging Protocol*

- Finalized imaging investigator team to ensure expertise and experience relevant to current protocol and findings
- Developed Technical Manual for neuroimaging protocol at MCW
- Ongoing meetings are conducted with imaging investigator team to ensure consistency of

protocol with ARC protocol, plan for data dissemination, and plan for data pipelining

- Finalized imaging modalities and specifications to mirror other large DoD- and NIH-funded research initiatives, including TRACK-TBI, ARC, and TBI Endpoints Development (TED) project to ensure ability for data integration across studies
- Developed advanced MRI informatics Pipeline Model for neuroimaging data acquisition, processing, transfer, storage, integration with larger dataset, analysis and dissemination, which includes implementation of an extensible neuroimaging archive toolkit (XNAT) database and use of Isilon server
- Deployed an automated quality assurance pipeline to verify imaging protocol compliance at the time of submission to the image archive
- Completed systematic review of current MR literature to assist in developing a stepwise approach to neuroimaging data analysis based on pre-defined hypotheses, core metrics, and analytical methods
- Engaged neuroradiologists to conduct systematic non-diagnostic review of anatomical images for incidental findings; automated system of notification, radiologic review within 24 hours, and procedures for communication of findings is fully operational
- Refined acquisition protocol after minor alterations were needed for DTI parameters and advanced prototype acquisitions were provided by GE Healthcare

#### *Subtask SA2 – Blood Biomarkers*

- Finalized candidate array of acute and subacute biomarkers for study
- Finalized protocol specifications for blood biomarker studies
- Cross-walked biomarker collection protocol with TRACK-TBI and ARC to ensure ability for data integration across studies
- Finalized standard operating procedures (SOP's) for blood biomarker collection, processing, shipping, analysis and storage
- Finalizing a stepwise approach to biomarker analysis with Banyan Biomarkers based on pre-defined hypotheses, core metrics, and analytical methods
- MCW Clinical and Translational Science Institute (CTSI) Translational Research Unit (TRU) and Banyan Biomarkers fully engaged in operationalizing blood biomarker protocol
- Biospecimen collection ongoing with samples currently stored at MCW TRU, samples to be shipped to Banyan engaging for analysis in Winter 2015-16

#### *Subtask SA3 – Head Impact Sensors*

- Teamed with ARC Head Impact Measurement (HIM) core team to conduct systematic review of head impact sensor option best suited for the current research project and the ARC.
- Retrieved size specifications for helmets and quantity of encoders needed from each institution for the Head Impact Telemetry System (HITS) and purchased all necessary equipment from Riddell
- Implemented HITS at 6 data collection sites for the Fall 2015 football season
- Evaluated existing data from our prior studies using X2 Biosystems xPatch to inform appropriate technology adoption for the current study
- Evaluated, as part of joint exercise of this study and ARC, other candidate non-helmeted head impact sensor options

- Continuing to evaluate available and emerging non-helmeted head impact sensor options ready and appropriate for use in research efforts, based on quality of validation, data upload infrastructure, and product production timeline
- Selected i1 Biometrics Vector Mouthguards for use in select subset of 75 athletes, MCW IRB approved Aug 24, 2015
- Two weeks after implementation, 3 research subjects came forward with chipped teeth while wearing research issued i1 Vector Mouthguard. PI initiated internal review process with research team, ARC HIM core team, and ARC PI's. Immediate decision was made to discontinue data collection using the i1 Vector mouth guard sensor. MCW IRB, HRPO and CDMRP scientific officers were notified of the situation and our recourse.
- Submitted brief formal review of head impact measurement work for this project and ARC to scientific officers (C. Vu, Ph.D; A. Hein, PhD)
- Developing stepwise approach to head impact measurement data analysis based on pre-defined hypotheses, core metrics, and analytical methods
- Conducting bi-weekly sessions with HIM team members to do detailed review of head impacts recorded in concussed athletes to assist in correlating HITS data with other study elements (clinical, neuroimaging, biomarker, genetics)
- Cross-walking data collection specifics to reflect ARC to ensure data integration across studies
- Continued engagement of MCW investigators key to head impact measurement element of study in planning around Pipeline Model for head impact measurement data acquisition, processing, transfer, storage, integration with larger dataset, analysis and dissemination
- Developing stepwise approach to head impact measurement data analysis based on pre-defined hypotheses, core metrics, and analytical methods
- Performed preliminary studies using existing datasets from prior funding cycles to quantify head impact exposure characteristics for different football positions and between games and practices, and highlighted the effects of head impact history on concussion tolerance

#### *Subtask SA4 – Genetic Testing*

- Engaged MCW TRU and MCW Tissue Bank in operationalizing genetic testing protocol
- Cross-walked protocol for genetic testing with ARC, identifying more detailed and expansive protocol for ARC
- As part of Kickoff Investigator Meeting, evaluated the benefits of revising current genetic testing protocol to be in line with ARC to ensure ability for data integration across studies
- Identified more detailed and expansive protocol for ARC genetic samples, in agreement with senior scientific advisory panel, decided to alter protocol to be an equivalent to ARC
- Obtained approval from grant science officer for operational change from buccal swab collection to blood collection for DNA extraction to align with ARC protocol
- Finalized new DNA extraction protocol specifications and operational plan for genetic testing
- Engaging local MCW lab for DNA extraction and Indiana University for consultation and analysis



- Samples from fall 2015 baseline testing processed and stored locally, will wait until the end of season for group analysis

<b>Major Task 3: Data Collection (post-IRB approval)</b>	<b>Months 7-48</b>
<p><i>Subtask 1 – Baseline Data Collection Protocol</i></p> <ul style="list-style-type: none"> <li>• Finalized baseline data collection protocol at Kickoff Investigator Meeting</li> <li>• Finalized data collection forms and manuals necessary for baseline testing</li> <li>• Successful baseline data collection on 545 athletes for the Fall 2015 season. Please see section 9 (Appendices) for a summary of the baseline sample characteristics.</li> </ul> <p><i>Subtask 2 – Postinjury Data Collection Protocol</i></p> <ul style="list-style-type: none"> <li>• Finalized postinjury data collection protocol at Kickoff Investigator Meeting</li> <li>• Finalized data collection forms and manuals necessary for post-injury testing</li> <li>• Accrual of post-injury data ongoing: From August 10, 2015 to September 29, 2015, 12 athletes with a concussion and 5 contact controls were enrolled (a total of 25 injured athletes and 15 contact controls enrolled by date of submission on October 29, 2015)</li> </ul> <p><i>Subtask 3 – Control Group Testing</i></p> <ul style="list-style-type: none"> <li>• Finalized protocol for contact sport controls data collection and matching of contact sport controls to injured athletes at Kickoff Investigator Meeting</li> <li>• Finalized protocol for non-contact sport controls data collection and matching of non-contact sport controls to injured athletes at Kickoff Investigator Meeting</li> <li>• Developed a matching algorithm similar to ARC protocol to quantify matching criteria of contact sport controls</li> <li>• Finalized protocol for normative neuroimaging atlas data collection protocol at Kickoff Investigator Meeting</li> <li>• Developed non-contact control screening form to best match non-contact sport athletes to concussed contact sport athletes</li> <li>• 11 atlas scans completed on contact sport athletes prior to season start which assisted in adjusting and refining MR protocol</li> <li>• Accrual of control data ongoing</li> <li>• Non-contact sport control data collection scheduled for Winter 2015-2016</li> </ul>	

<b>Major Task 4: Data Management, Analysis &amp; Dissemination</b>	<b>Months 7-48</b>
<p><i>Subtask 1 – Data Management</i></p> <ul style="list-style-type: none"> <li>• Electronic REDCap database for project finalized and developed based on final protocol and core data elements</li> <li>• Developed architectural plan for integration of core data elements from all protocol components (neuroimaging, head impact measurement, biomarkers, genetic testing) with clinical data in REDCap database</li> <li>• Developed architectural plan for connectivity between central REDCap database and repositories holding larger raw data sets from all protocol components (neuroimaging, head impact measurement, biomarkers, genetic testing)</li> </ul>	

- Installed major information technology (IT) storage and processing hardware to support this work at MCW, including new EMC Isilon 5 system
- Protocols and standard operating procedures for data quality review and management adopted, in accordance with current study requirements and existing procedures
- Developed separate databases and repositories to hold larger raw datasets from neuroimaging and head impact measurement cores
- Finalizing plan for connectivity between central REDCap database and repositories holding larger raw data sets from all protocol components (neuroimaging, head impact measurement, biomarkers, genetic testing)
- Core data elements for current study continually cross-walked with ARC as changes in ARC occur
- Hired, and trained full time staff member who is dedicated to data quality assurance procedures and development and implementation of procedures to push study data to FITBIR
- Continued communication with Federal Interagency TBI Research (FITBIR) Informatics System to discuss study design, NINDS common data elements (CDE), and eventual process for data transfer to FITBIR; currently developing UDEs and merging CDEs from our dataset
- Data quality control plan reviewed and revised from existing procedures to handle all data elements

#### *Subtask 2 – Data Analysis*

- Developing pre-defined core metrics and analytical plan to test specific hypotheses within each study core (clinical, head impact measurement, neuroimaging, blood biomarkers, and genetic testing)
- Aligned proper subject matter expertise on the investigative team to contribute to data analysis in respective study cores

#### *Subtask 3 – Dissemination*

- At Kickoff Investigator Meeting, identified possible “early wins” for publication of interim study findings appropriate for dissemination over life the project, rather than waiting until full completion of data collection
- List of priority papers, posters, presentations, etc. in ongoing development for execution with appropriate level of data collection
- Continued meetings and discussions with subject matter experts and investigative team to develop analytic plan for dissemination

### **What opportunities for training and professional development has the project provided?**

Nothing to Report

### **How were the results disseminated to communities of interest?**

Nothing to Report

## What do you plan to do during the next reporting period to accomplish the goals?

To continue our on-time progress toward accomplishment of the major tasks and subtasks for this project, we plan and will prioritize the following objectives during the next reporting period:

1. **Head Impact Measurement Protocol:** The following tasks are prioritized:
  - a. *Non-helmeted Sensor Technology:* We will continue to evaluate non-helmeted sensors for Fall 2016 after our discontinuation of the i1 Biometrics Vector mouth guard in Fall 2015. Once suitable options have been presented for non-helmeted sensors, we will perform laboratory validation and follow a similar deployment scheme for on-field validation to the i1, which will involve limited deployment in our local study prior to use in the ARC. While this will limit data collection for the current year, we have some confidence that either the new X2 sensor will be available or we can understand and remedy issues with i1 during calendar year 2016.
  - b. *Pipeline:* We will finalize the integration of head impact measurement data with larger dataset, analysis and dissemination prior to implementation to ensure accuracy.
  - c. *Quality Control:* We will continue our implementation of a multi-level model for monitoring and evaluating data quality.
2. **Advanced Neuroimaging Protocol:** The following tasks are prioritized:
  - a. *Imaging Pipeline:* We will expand the automated procedures implemented in the XNAT database to further ensure quality by auditing data transfer and redundant storage, as well as by computing modality-specific quality control metrics. Work will continue to develop further advanced simultaneous multi-slice diffusion acquisitions, which are amenable to heavier subjects, like many of those included in this study.
  - b. *Image Processing Pipelines:* We will deploy scripted algorithms for standard, modality specific image and time series processing procedures and coupled human algorithms to ensure accuracy in processing
  - c. *Analytics:* We will continue the initial analysis of complimentary neuroimaging data sets to develop analytic models to test with the independent data acquired in this project, driving integration with the larger dataset. This process will continue development of a stepwise approach to neuroimaging data analysis based on pre-defined hypotheses, core metrics, and analytical methods to achieve our specific aims while allowing flexibility to adjust according to our findings without introducing an intra-sample bias.
3. **Blood Biomarker Protocol:** The following tasks are prioritized:
  - a. *Initial Analysis:* We plan to ship the Fall 2015 baseline samples to Banyan Biomarkers for initial analysis in Winter 2016. Post-injury and control samples will be analyzed in batch when more cases have complete post injury data sets.
  - b. *Analytics and Dissemination:* We will continue development of a stepwise approach to biomarker analysis based on pre-defined hypotheses, core metrics, and analytical methods to achieve our specific aims.

4. **Genetic Testing Protocol:** The following tasks are prioritized:
  - a. *DNA Collection:* We will continue to work with MCW TRU, Tissue Bank and Indiana University to finalize our DNA collection and extraction protocol.
  - b. *Analytics:* We will continue development of a stepwise approach to DNA analysis based on pre-defined hypotheses, core metrics, and analytical methods to achieve our specific aims.
5. **Postinjury Data Collection:** We will continue our current enrollment and evaluate weekly to ensure we are on track to reach our specific aims. We will begin enrolling non-contact sport controls during the next reporting period.
6. **Data Management:** the following tasks are prioritized:
  - a. *Database:* We will continue to refine the architecture and function of our electronic REDCap database according to the protocol specification and required data elements, in parallel to the same for the ARC, in compliance with the NINDS CDE and in preparation for data transfer to FITBIR.
  - b. *FITBIR:* We will continue to work with FITBIR representatives to operationalize and refine our platform and process that facilitates data transfer from our REDCap system to FITBIR. We now have a dedicated staff member assigned to the FITBIR data management priority, who is now fully engaged with FITBIR. Our dedicated lab resource will continue working with FITBIR representatives and the team submitting data for ARC to create UDEs and merge existing UDEs into our dataset.
  - c. *Quality Control:* We will continue to develop and implement processes to monitor data quality associated with all aspects of the protocol (clinical testing, head impact measurement, neuroimaging, biomarkers, genetic testing).

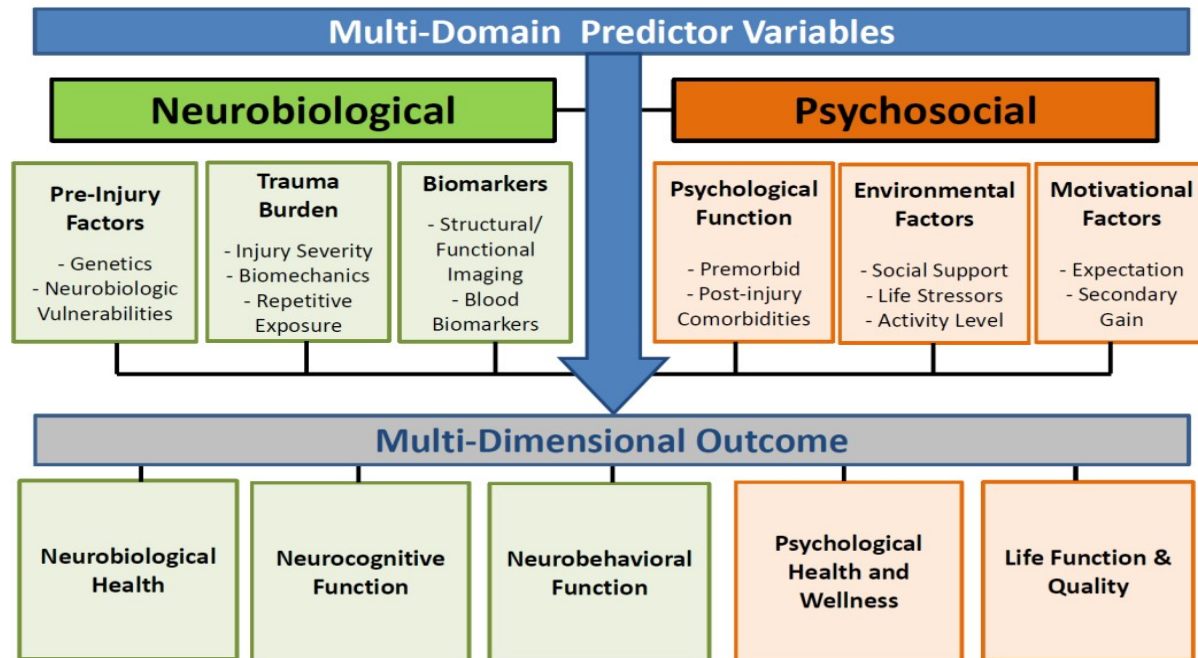
#### 4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

##### COMPREHENSIVE APPROACH TO STUDY OF TBI

Most importantly, this study will allow us to investigate the correlation between multi-dimensional predictor and outcome variables associated with mTBI from a fully neurobiopsychosocial perspective *in a common injured sample and single study design* (see **Figure 1**). This work will enable a longitudinal perspective on factors that influence both short-range and long-term outcomes after mTBI, and will foster DoD-funded collaboration aimed at informing the broader science of mTBI in military, sports and civilian populations.

**Figure 1. Neurobiopsychosocial Model of mTBI**



#### **ADVANCED TECHNICAL DEVELOPMENT:**

*Our investigative team of TBI researchers and imaging scientists has collaboratively developed a cutting-edge, multi-modal MRI protocol targeted specifically at the pathophysiology of SRC and mTBI that will provide benefit to the TBI research community.*

Our MRI protocol combines conventional anatomical imaging with advanced, motion compensated MRI acquisition techniques, diffusion kurtosis/tensor imaging (DKI/DTI), susceptibility weighted imaging (SWI) and quantitative susceptibility mapping (QSM), resting state metrics of functional connectivity (rs-fMRI), and blood flow imaging with arterial spin labeling (see **Table 1**). The protocol features a multi-band (8x) accelerated pulse sequence that achieves a high sampling rate while retaining high spatial resolution (2mm isotropic) for robust signal detection in rs-fMRI that is consistent with acquisitions in Human Connectome Project related studies. In addition, we have deployed three advanced pulse sequences and associated innovative data processing and modeling tools that show promise as diagnostic and prognostic biomarkers for diffusion kurtosis imaging (DKI), quantitative susceptibility mapping (QSM), and 3D arterial spin labeling (ASL).

**Table 1. MCW Multi-Modal MRI Protocol for Acute Sport-Related Concussion**

Targeted Modality	Acquisition Protocols	Reconstruction Requirements	Acquisition Time
	Localizer	Standard	0:30
	Sensitivity map generation	Standard	0:30
Cerebral blood flow	3D enhanced ASL prototype	Standard, flow, transit time corrected flow	4:36
Micro hemorrhage & gray-white matter transition	SWI/QSM (2x1 ARC) prototype	Standard SWI, offline “Orchestra” phase-based imaging and QSM	4:00
Anatomy, gray-white matter segmentation	PROMO MPRAGE prototype	Standard	4:11
Anatomy, edema detection	PROMO T2 FLAIR prototype	Standard	4:42
Anatomy, pial surface segmentation	PROMO T2 prototype	Standard	4:12
White matter integrity & microstructure	DTI/DKI	Standard DTI, offline post-processing of DKI from standard DICOM images, including distortion correction	5:30
	DTI-Distortion Cal		0:30
Resting state functional connectivity	rs-fMRI with multi-band prototype acquisition (human connectome project harmonized)	Offline “Orchestra” multi-band reconstruction (auto-calibration, slice-GRAPPA unaliasing)	6:00
	rs-fMRI-Distortion Cal	Offline, used for rs-fMRI distortion correction	0:30
Myelin mapping	Inhomogenous broadened magnetization transfer (IhMT) prototype	Standard, quantified MT, quantified IhMT	4:48
Total Acquisition Time:			40:00

The technical implementation of this innovative TBI imaging protocol has been highly successful based on:

- *Engagement:* This project represents a major collaborative, multidisciplinary effort by highly skilled imaging and neuroscience researchers at MCW.
- *Scanning time:* 40-minute acquisition time.
- *Compliance:* Athletes respond favorably to the procedures and short scanning session.
- *Quality Control:* High resolution imaging with minimal technical error or artifact.
- *Automation:* Customized protocol is essentially a turn-key option for scanner operators.
- *Analytics:* Customized analysis procedures unique to each pulse sequence and modality.
- *Translation:* Targeted modalities and pulse sequences capable of rollout in clinical settings.

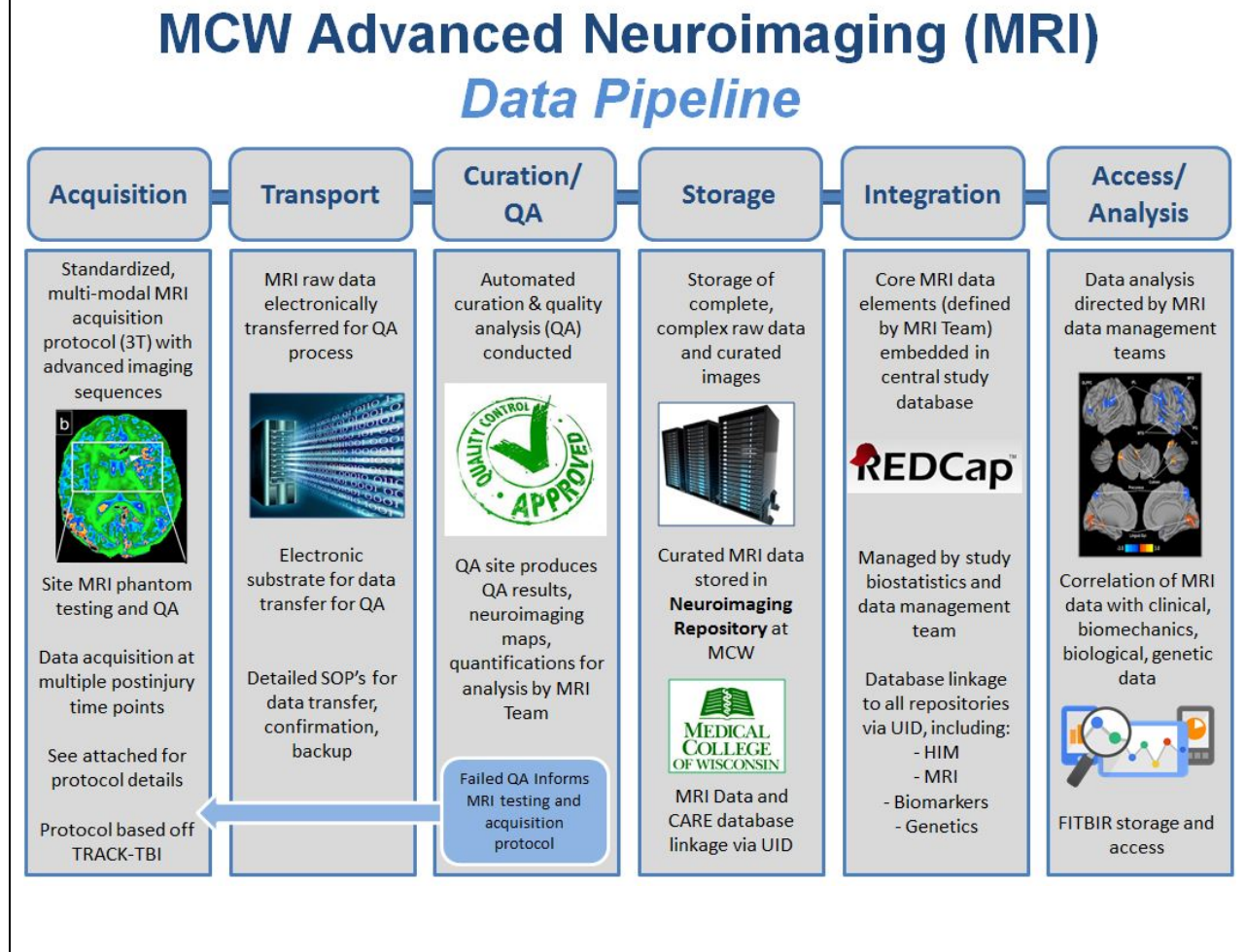
We have cross-walked our MRI acquisition protocol with the GE Research Protopak I/II for TBI and the acquisition protocols for other large research networks such as TRACK-TBI (G. Manley, PI) in order to facilitate eventual sharing/merging of like-set imaging data and enable comparisons of TBI imaging biomarkers across populations at risk (civilians, athletes, military service members). This exercise indicates a high degree of overlap between study protocols. We have merged our acquisition developments with the GE Healthcare traumatic brain imaging “Protopak 2” content to further build cross-study compatibility. This paves the way for further optimization of innovative MRI protocols to be included in other large-scale, national TBI research efforts (e.g., NCAA-DoD Grand Alliance).

## POWERFUL IMAGING PIPELINE AND INFORMATICS PLATFORM

*Our work supported the development and construction of a technologically advanced platform for MRI post-processing, analytics, transfer and storage that provides a powerful engine to support and accelerate our future research efforts toward advancing the science and clinical utility of MRI biomarkers for concussion and TBI.*

Although not initially proposed in this work, the development of an imaging informatics infrastructure has been part of this first year's progress. Each imaging session includes 12 series, 11,130 images, and over 10 gigabytes of data. Further, a subset of the prototype acquisitions, including the simultaneous multi-slice resting state fMRI and the quantitative susceptibility mapping series require off-line reconstruction of the raw k-space "p-files." With enrollment proceeding as expected and four imaging sessions for each subject, along with a large group of collaborating investigators, a central, organized, automated, and accessible database solution was required. **Figure 2** illustrates the stepwise architecture of our "pipeline" for imaging acquisition, transport, curation and quality control, storage, analysis and integration with other rich clinical datasets (see **Figure 2**). This approach was modeled after centers leading other large research efforts employing advanced MRI in the study of concussion and TBI, such as TRACK-TBI (G. Manley, PI).

**Figure 2. MCW Advanced Neuroimaging Pipeline**



The eXtensible Neuroimaging Archive Toolkit (XNAT, [www.xnat.org](http://www.xnat.org)) was selected to serve as the central repository for this work (**Figure 3**). XNAT offers a number of compelling features that make it ideally suited for this job. A web-based user interface facilitates team member access to the repository, which is organized hierarchically by project, subject, session and series. DICOM images acquired on the research-dedicated MCW Discovery MR750 can be directly pushed to a DICOM listener integrated into the XNAT deployment, and then automatically integrated into the image database, or archived data sets may be uploaded through the web interface. Underlying the web interface is a PostgreSQL database that can be accessed through a representational state transfer application program interface (REST API). This powerful architecture enables programmatic queries of the image and metadata database and scripting of custom processing pipelines. We have built a Python interface for scripting XNAT processing through the REST API. Work is ongoing to further integrate raw “p-file” storage and automatic Orchestra-based p-file reconstruction via “son of recon” programs automatically initiated by the acquisition pulse sequence through this XNAT REST API. While processing pipelines are prototyped outside of the XNAT framework, finalized pipelines are to be integrated into the XNAT service to further streamline data processing.

**Figure 3: MCW XNAT Web Interface for this Brain Injury Research**

The screenshot displays the MCW XNAT Web Interface. At the top, there is a search bar and navigation links: Home, New, Upload, Administer, Tools, and Help. The main content area is titled 'MCW General Electric Healthcare Head Health Challenge I'. It features tabs for Details, Access, Manage, and Pipelines. The 'Details' tab is selected, showing the following information:

- ID:** GEHHC1
- Description:** 2014-2015 mTBI project. PI is Mike McCrea. Scans of concussed athletes (24 hrs, 7 days, 6 months) include SPGR, SMS resting state, DKI, QSM, and ASL.
- PI:** McCrea, Mike
- Investigators:** Nencka, Andrew ; Koch, Kevin ; Muftuler, Tugan

Below the details are buttons for 'Edit Details', 'Delete', and 'Manage Custom Variables'. On the right side, there is an 'Actions' menu with options: Add, Upload Images, View Prearchive, Scan Type Cleanup, Add to Favorites, Download XML, Download Images, and Manage Files.

The 'Subjects' tab is also visible, showing a table of subjects. The table has columns: Subject, M/F, Hand, YOB, Control, SCAT3Score, InjuryDate, and MR Sessions. The table contains 5 rows of data.

Subject	M/F	Hand	YOB	Control	SCAT3Score	InjuryDate	MR Sessions
01010088	U						3
01010110	U						2
01010119	U						4
01010125	U						3
01010128	U						2
01010137	U						3

This XNAT deployment is, in practice, a constellation of computing hardware installed in the MCW Research Computing Center. Three separate servers are each running an instance of XNAT, including a gateway server for data transfers with off-site collaborators and a pair of servers to host redundant XNAT instances of the central database. Images in the central database are stored on an 860 Tb Isilon storage system, which is backed up through snapshots, mirroring to an additional Isilon storage system, and magnetic tape archiving. The XNAT deployment is



further designed to offload processing intensive tasks to other resources of the MCW Research Computing Center, including a 408-core MPI cluster, a large (3Tb) memory system, and four general purpose graphical processing unit (GPU) systems, each with four Nvidia K40 GPUs. Each of these computing units are interconnected with 10 gigabit Ethernet, while internal communication for each unit is maintained with infiniband connections. The XNAT servers are further connected to the general MCW network and pass through the Froedtert Hospital firewall for direct DICOM image pushes to the McKesson PACS for over reads of selected image series.

The XNAT deployment is being further extended to support other mTBI studies at MCW, including the Advanced Research Core of the NCAA/DoD CARE project and the locally conducted GE-NFL Head Health Challenge phases I and II. Reciprocally, data to be acquired in ongoing projects will be used to further refine the data handling and processing software deployed in XNAT. Through this work, MCW will ultimately host the definitive sport related concussion imaging database in this XNAT deployment.

#### **What was the impact on other disciplines?**

Nothing to Report

#### **What was the impact on technology transfer?**

Nothing to report at this time, although we anticipate that our efforts toward building a unique technologically advanced TBI MRI informatics system has great potential for technology transfer and product deployment in the future.

#### **What was the impact on society beyond science and technology?**

The current study proposal enables a fully integrated and comprehensive investigation of a multidimensional set of injury predictor and diagnostic variables such as *pre-injury function* (e.g. cognitive, behavioral, and psychosocial function, genotype), *injury biomechanics and dynamics* (e.g. mechanism, severity, frequency, associated injury), *immediate post-injury characteristics* (e.g. acute biological, structural and functional markers), and *longitudinal follow-up* (e.g. true natural history of biological, physiological and clinical recovery). In parallel, the aims of this proposal align directly with the DoD's priorities to develop evidence-based approaches to improving the medical care, health and welfare of our military service members affected by TBI. The findings of this study are expected to directly impact the current and future state of military medicine relevant to the diagnosis, treatment and prevention of mTBI in military service members. To date, we lack an integrated neurobiopsychosocial model of mTBI in civilians that can effectively guide evidence based approaches to best practice in the diagnosis, assessment and management of persons affected by mTBI. The proposed work will foster several lines of collaboration with other DoD-funded investigators conducting innovative TBI research, all aimed at informing the broader science of mTBI in military, sports and civilian populations. This study is designed to significantly advance our understanding of mTBI in such a way to not only benefit the military and sports medicine sectors, but also improve care for patients in our society affected by mTBI.

## 5. CHANGES/PROBLEMS:

### Changes in approach and reasons for change

**Genetics Collection:** Prior to the initiation of baseline data collection, we requested to change from a buccal-based (cheek swab/saliva) collection to a blood draw for the genetics protocol. This change was made in order to maintain sample collection consistency and comparability to other major TBI Studies funded by MRMC (e.g. NCAA-DoD Grand Alliance ARC).

**Head Impact Sensor Technology:** Two non helmet-based head impact measurement options most suited to the present study (X2 and i1) have issues that are currently preventing implementation. The X-Patch has demonstrated suitable validation on a crash test dummy but suffers when used on humans due to skin laxity, which prevents rigid fixation to the skull. Additionally, the previous version of the X-Patch has been discontinued for a smaller model that may not have the same inertial effects and has the possibility of incorporation in a mouth guard. However, the newer version has not been released and would require significant laboratory validation prior to incorporation in the current study.

An alternative is the i1 mouth guard system, which has also demonstrated suitable validation in limited experimental studies. We deployed these sensors in football players during the Fall 2015 season. However, we had to discontinue their use due to issues with players' teeth chipping during use. This apparently has not been an issue in other deployments of the i1, but we chose to discontinue after 3 of our 75 players developed chipped teeth during use. We are working with i1 to understand this issue. Other non helmet-based systems are not commercially ready and/or do not have a proper data transfer interface that is required for this study.

We are continuing to explore options for a non helmet-based sensor but will not be deploying another non-helmeted sensor for fall 2015. This is due to the lack of a suitable option that has a suitable research infrastructure and has been validated in the laboratory. Once a suitable option has been presented for non-helmeted sensors, we will explore laboratory validation and follow a similar deployment scheme for on-field validation to the i1. While this will limit data collection for the current year, we have some confidence that either the new X2 sensor will be available or we can understand and remedy issues with i1 during calendar year 2016.

### Actual or anticipated problems or delays and actions or plans to resolve them

**Head Impact Sensor Technology:** As indicated previously, we continue to encounter challenges in identifying non-helmeted head impact sensors that a) have proper level of preliminary validation to support their use in research efforts, b) have a platform for large scale production to meet our needs, and c) are feasible for field use (with acceptable athlete compliance). We continue to evaluate all options for non-helmeted sensors focusing on both the safety of athletes and accuracy of data collection.

**IRB Approval Timeline:** The strategy to prioritize the ARC IRB review to facilitate the IRB's review of the current protocol and informed consent form resulted in a slight delay in our submission and review process. The slight delay did not jeopardize our data collection timeline or overall project schedule.

### **Changes that had a significant impact on expenditures**

We are currently underspending for this project, due to a combination of factors outlined below. We anticipate that spending for the overall period of performance for the project will come in at budget. The following changes had an impact on spending during the current reporting period:

- Salaries & Fringe
  - We did not conduct baseline testing in Spring 2015 which resulted in a surplus baseline technician hours.
  - One of our FTE Research Assistants left in Aug 2015, and we have not refilled the position to date.
  - We have not filled Imaging Postdoc role.
  - The biomechanics technicians require less time to manage only one head impact sensor system at their respective sites.
- Equipment
  - Funds will be used over years 2-3 to pay for Isilon server purchase.
- Supplies
  - Other than small amount to purchase il mouth guard system, we have not used the majority of funds budgeted for non-helmeted sensor system.
- Travel
  - There has been no conference or IPR attendance travel to date.
- Subcontracts
  - Banyan subcontract period of performance did not start until Jan 1, 2015. Costs were shifted into years 2-3.

### **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

#### **Significant changes in use or care of human subjects**

- DNA extraction changed from buccal swab collection to blood draw prior to study implementation. Approved by MCW IRB and HRPO on June 2, 2015.
- Head impact sensor company changed prior to study implementation and MCW IRB provided oversight for Banyan Biomarkers' research activities. Approved by MCW IRB Aug 24, 2015.
- Reportable Events submitted to MCW IRB:
  1. Unanticipated reaction to a blood draw on one subject, similar to a vasovagal response. Acknowledged by MCW IRB on Aug 3, 2015 and reported to HRPO.
  2. Athlete wore helmet with head impact sensor without signing consent. Acknowledged by MCW IRB on Aug 28, 2015.
  3. TRU nurse drew 3 tubes of blood instead of 2 at first post injury time point on 2 subjects. Acknowledged by MCW IRB on Sept 4, 2015.

4. Subject wore a helmet with a head impact sensor installed prior to signing a consent form. He was aware of the study and agreed to participate and completed the rest of study procedures on Aug 21, 2015. He signed a consent form on Aug 17, 2015, but he did wear the helmet for one practice prior to signing. Acknowledged by MCW IRB on Sept 4, 2015.
5. Subject obtained a blood draw before signing a consent form. He was aware of the study and knew all details about the study, but he stopped at the blood draw station first and we were unaware). He signed the consent form 2 minutes after the draw. Acknowledged by MCW IRB on Sept 4, 2015.
6. First incident of chipped tooth while wearing i1 mouth guard. Acknowledged by IRB on Sept 14, 2015.
7. Two additional incidences of chipped teeth while wearing i1 mouth guard. Under full committee review as of Sept 29, 2015.

**Significant changes in use or care of vertebrate animals**

Not applicable

**Significant changes in use of biohazards and/or select agents**

Not applicable

**6. PRODUCTS:**

- **Publications, conference papers, and presentations**

**Journal publications.**

Nothing to report for the current reporting period; data collection still underway. Priority papers pending more data collection. Plan is to analyze and disseminate findings as appropriate over life of the project, as appropriate and indicated, not necessarily waiting until full study completion.

**Books or other non-periodical, one-time publications.**

Nothing to report for the current funding period

**Other publications, conference papers, and presentations.**

Nothing to report for the current reporting period; data collection still underway. Priority papers pending more data collection. Plan is to analyze and disseminate findings as appropriate over life of the project, as appropriate and indicated, not necessary waiting until full study completion.

- **Website(s) or other Internet site(s)**

Nothing to report for the current funding period

- **Technologies or techniques**

Please see section 4 (Impact) above on MR imaging informatics platform technologies developed as part of this effort.

- **Inventions, patent applications, and/or licenses**

Nothing to report for the current reporting period

- **Other Products**

1. REDCap database built for clinical data collection, being refined for MR, head impact measurement, and blood/genetic data.
  - a. Our REDCap database for this study will be leveraged to facilitate a project led by the NINDS toward development of Common Data Elements (CDE) for sport-related concussion.
2. XNAT database platform developed for neuroimaging raw data.
3. Custom database platform designed for head impact measurement raw data.
4. EMC Isilon server set up for data storage.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

### What individuals have worked on the project?

Our investigative team for the current project includes clinical and scientific experts within and across all core elements of the study, including clinical, head impact measurement, neuroimaging, biomarkers, and genetic testing. In addition to our key personnel, we have engaged subject matter experts from the ARC investigative team to ensure proper linkage between the two projects for purposes of protocol synchronization and eventual data integration. The following list includes all personnel contributing to work associated with the current project, regardless of funding source.

Name	Project Role	Percent Effort	Contribution to Project
Michael McCrea, PhD	PI	25%	Oversight of project, responsibility for scientific integrity, operational execution, fiscal performance
Lindsay Nelson, PhD	Co-I, Clinical Core	20%	Project design and execution; Database engineering and refining the clinical protocol

Timothy Meier, PhD	Neuroscience Faculty, MRI & Biomarker Cores	20%	Implementation of protocol for multi-modal MRI data and biomarker acquisition, processing, storage, integration, and analysis
Melissa Lancaster, PhD	Clinical Post-doc	25%	Execution, processing and analysis associated with clinical and neuroimaging studies
Andrew Nencka, PhD	Imaging Faculty, MRI Core	15%	Lead technical expert on multi-modal MRI protocol for current study; Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
Shi-Jiang Li, PhD	Co-I, MRI Core	7.5%	Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
Matthew Budde, PhD	Co-I, MRI Core	2.5%	Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
Kevin Koch, PhD	Imaging Faculty, MRI Core	5%	Technical lead for ARC MRI core and liaison to current study; Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
L. Tugan Muftuler, PhD	Imaging Faculty, MRI Core	5%	Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
Yang Wang, MD, PhD	Imaging Faculty, MRI Core	3%	Development and implementation of protocol for multi-modal MRI data acquisition, processing, storage, integration, and analysis
Ron Hayes, PhD	Co-I, Banyan Biomarkers, Biomarker Core	5%	Development and implementation of protocol for biomarker collection, processing, storage, integration, and analysis
Brian Stemper, PhD	Co-I, Head Impact Measurement Core	5%	Co-lead of ARC head impact measurement (HIM) core; assist in development and implementation of protocol for head impact measurement data acquisition, processing, storage, integration, and analysis
Alok Shah, MS	Engineer, Head Impact	18%	Development and implementation of protocol for HIM data acquisition,

	Measurement Core		processing, storage, integration, and analysis
John Humm	Engineer, Head Impact Measurement Core	2.5%	Assist in development and implementation of protocol for HIM data acquisition, processing, storage, integration, and analysis
Jennifer Hill, MA, CCRC	Program Manager, Project Coordinator	50%	Operational and fiscal management of project
Katie Krahn	Program Coordinator	20%	Support project functions related to participant scheduling, reimbursement, inventory management
Ashley LaRoche, CCRC	Study Coordinator	90%	Operational coordination of project, regulatory and IRB processes, protocol implementation
Melissa Koschnitzke, MA, CCRC	Research Coordinator	10%	Assisting in protocol planning and operations
Robyn Furger, MA CCRC	Research Coordinator	10%	Assisting in protocol planning and operations
Adam Pfaller	Research Assistant	50%	Assisting in protocol planning and operations
Abby Klemp	Research Assistant	30%	Data collection and entry
Mary Gonring	Research Assistant	30%	Data collection and entry
Amy Nader	Research Assistant	30%	Data Collection and entry
Daniel Huber	Research Technologist	50%	FITBIR liaison and data quality specialist

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

W81XWH-12-1-0004, Log No. 11074005 (PI: McCrea) ended on 8/31/2015.

**What other organizations were involved as partners?**

Organization Name	Location	Contribution to the Project
Froedtert Hospital	Milwaukee, WI	Facilities
Zablocki VA Medical Center	Milwaukee, WI	Facilities, Collaboration
Banyan Biomarkers, Inc.	Alachua, FL/San Diego, CA	Collaboration
Indiana University	Indianapolis, IN	Collaboration

Carroll University	Waukesha, WI	Facilities, Collaboration
Concordia University of Wisconsin	Mequon, WI	Facilities, Collaboration
Carthage College	Kenosha, WI	Facilities, Collaboration
Wisconsin Lutheran College	Milwaukee, WI	Facilities, Collaboration
Franklin High School	Franklin, WI	Facilities, Collaboration
Marquette University High School	Milwaukee, WI	Facilities, Collaboration
Wauwatosa East High School	Wauwatosa, WI	Facilities, Collaboration
Whitefish Bay High School	Whitefish Bay, WI	Facilities, Collaboration

## 8. SPECIAL REPORTING REQUIREMENTS

**QUAD CHARTS:** If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.

Please see Quad Chart on following page.



# Comprehensive study of acute effects and recovery after concussion

Log No: 13114003

Award No: W81XWH-14-1-0561

PI: Michael McCrea, PhD, ABPP

Org: The Medical College of Wisconsin, Inc. Award Amount: \$5.5M

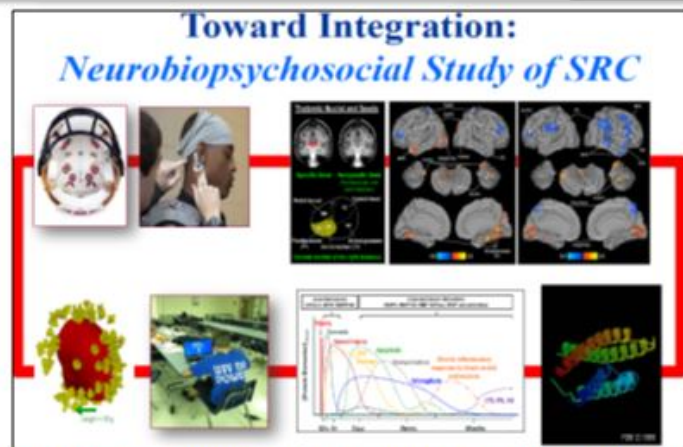


## Study Aims

- Conduct advanced, multimodal MRI studies at multiple time points during the acute and subacute phase after mTBI.
- Collect and analyze blood biomarkers at baseline and multiple time points during the acute and subacute phase after concussion.
- Dually-equip high school and collegiate athletes with the HIT System and/or non-helmet head impact sensors.
- Conduct genetic testing in our pre-exposure baseline assessments of athletes.

## Approach

This study enables a fully integrated and comprehensive investigation of a multidimensional set of injury predictor and diagnostic variables such as *pre-injury function* (e.g. cognitive, behavioral, and psychosocial function, genotype), *injury biomechanics and dynamics* (e.g. mechanism, severity, frequency, associated injury), *immediate post-injury characteristics* (e.g. acute biological, structural and functional markers), and *longitudinal follow-up* (e.g. true natural history of biological, physiological and clinical recovery).



This study will investigate the correlation between multi-dimensional predictor and outcome variables associated with mTBI from a fully neurobiopsychosocial perspective in a common injured sample and single study design.

## Timeline and Cost

Activities	CY	14	15	16	17
Project Contracting & Regulatory					
Operationalize Protocol					
Data Collection					
Data Management, Analysis & Dissemination					
<b>Estimated Budget (\$5.5M)</b>		<b>\$225K</b>	<b>\$2.19M</b>	<b>\$1.62M</b>	<b>\$1.47M</b>

Updated: 10/29/2015

## Goals/Milestones

### Major Task: Project Contracting & Regulatory

- Approval received from MCW IRB and HRPO for Banyan activities
- Amendments and Reportable Events submitted to MCW IRB & HRPO

### Major Task: Operationalize Protocol

- Ongoing protocol refinement with investigators from each core area as needed

### Major Task: Data Collection:

- 545 athletes baseline tested; enrolled 25 injured and 15 contact controls in post injury protocol as of 10/29/15

### Major Task: Data Management, Analysis & Dissemination

- Continued refinement of data pipeline for each core area
- Hired full time staff member to coordinate data transfer to FITBIR

### Comments/Challenges/Issues/Concerns

- Challenges encountered in availability of validated non-helmeted head impact sensor systems; current evaluating validated options available to ensure proper resource utilization

### Budget Expenditure to Date

Projected Expenditure: \$ 2.01M Actual Expenditure: \$ 1.34M

## 9. APPENDICES:

**Table 2. Study Technical Objectives and Specific Aims**

The current study proposal enables a fully integrated and comprehensive investigation of a multidimensional set of injury predictor and diagnostic variables such as *pre-injury function* (e.g. cognitive, behavioral, and psychosocial function, genotype), *injury biomechanics and dynamics* (e.g. mechanism, severity, frequency, associated injury), *immediate post-injury characteristics* (e.g. acute biological, structural and functional markers), and *longitudinal follow-up* (e.g. true natural history of biological, physiological and clinical recovery).

<b>ADVANCED NEUROIMAGING BIOMARKERS:</b>	<p><b><u>Technical Objective:</u></b> To conduct advanced, multimodal MRI studies at multiple time points during the acute and subacute phase after mTBI.</p> <p><b><u>Specific Aims:</u></b></p> <ol style="list-style-type: none"> <li>1. Characterize the physiological effects of acute mTBI on brain structure and function.</li> <li>2. Determine how the natural time course of neurophysiological recovery after mTBI compares to the time course of clinical recovery.</li> <li>3. Determine the window of neurophysiological vulnerability after mTBI, during which the brain is at risk of secondary or cumulative injury.</li> </ol>
<b>BLOOD BIOMARKERS:</b>	<p><b><u>Technical Objective:</u></b> To collect and analyze blood biomarkers at baseline and multiple time points during the acute and subacute phase after concussion.</p> <p><b><u>Specific Aims:</u></b></p> <ol style="list-style-type: none"> <li>1. Measure the direct effects of acute mTBI on brain biology.</li> <li>2. Correlate the sensitivity and specificity of brain biomarkers with other measures of the effects of mTBI (symptom recovery, cognitive testing, balance assessment, neuroimaging).</li> <li>3. Determine how the time course of biological recovery after mTBI compares to the time course of clinical recovery.</li> </ol>
<b>HEAD IMPACT SENSORS:</b>	<p><b><u>Technical Objective:</u></b> To dually-equip high school and collegiate athletes with the HIT System and/or non-helmet head impact sensors.</p> <p><b><u>Specific Aims:</u></b></p> <ol style="list-style-type: none"> <li>1. Cross validate multiple head impact sensors systems used in mTBI research.</li> <li>2. Measure the relationship between biomechanical metrics of head impact location and magnitude (e.g., rotational acceleration) and measures of clinical and physiological effects of acute mTBI.</li> <li>3. Determine the minimum biomechanical threshold sufficient to cause mTBI.</li> <li>4. Determine the clinical effects of subconcussive head impact exposure from contact and collision sports on neurocognitive function through comparison to a noncontact sport control group not exposed to repetitive head impacts.</li> </ol>
<b>GENETIC TESTING:</b>	<p><b><u>Technical Objective:</u></b> To conduct genetic testing in our pre-exposure baseline assessments of athletes.</p> <p><b><u>Specific Aims:</u></b></p> <ol style="list-style-type: none"> <li>1. Determine the influence of genetics on risk of mTBI.</li> <li>2. Determine genetic influence on acute recovery and outcome after mTBI.</li> <li>3. Enable longitudinal study of the influence of genetics on long-term outcome after mTBI in a well characterized cohort of injured and control subjects.</li> </ol>

**Table 3. Baseline Sample Demographics**

	<i>N</i> = 545
	<i>M</i> ( <i>SD</i> ) or %
Gender (% Male)	100.0%
Age (years)	18.60 (1.79)
Level of competition (% College)	79.0%
Race	
White	79.4%
Black	16.4%
Asian	0.9%
Native Hawaiian/Pacific Islander	0.2%
Other/Unknown	2.8%
Height (inches)	71.56 (2.79)
Weight (pounds)	206.28 (42.56)
Grade point average	3.11 (.50)
WTAR standard score	100.23 (13.12)
Number of prior concussions	.75 (1.29)
ADHD	8.0%
Learning disability	2.0%

*Note.* WTAR = Wechsler Test of Adult Reading standard score; ADHD = attention deficit-hyperactivity disorder.